DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

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Food and Drug Administration
Denver District Office
Building 20 - Denver Federal Center
P. O. Box 25087
Denver, Colorado 80225
TELEPHONE: 303-236-3000

August 25, 1998

WARNING LETTER

HAND DELIVERED

Mr. Mats Wahlstrom
President
GAMBRO Healthcare, Inc.
1185 Oak Street
Lakewood, Colorado 80215

Dear Mr. Wahlstrom:

During the Food and Drug Administration's (FDA) recent inspections at four facilities of GAMBRO Healthcare, Inc., (GAMBRO) located at Lakewood, Colorado, your corporate headquarters facility, (inspected June 17-July 8, 1998); COBE Renal Care de Mexico, Tijuana, Mexico, (inspected June 1-10, 1998); GAMBRO Healthcare, Inc., Newport News, Virginia, (inspected June 15-July 17, 1998); and GAMBRO Healthcare, Inc., DeLand, Florida, (inspected May 26- June 10, 1998); our investigators determined that your firm manufactures dialysis equipment and supplies which includes but is not limited to blood tubing sets and dialysate. These products are devices within the meaning of Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The purpose of this letter is to apprise top management of the observations made at your corporate facilities, and to remind you of your involvement and responsibility to assure all corporate facilities are in compliance with the Act and all pertinent regulations. FDA is concerned about the breadth and scope of the specific violations noted in this letter and in the inspectional observations noted on form FDA-483s issued at the close of the above mentioned inspections which we believe are symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

As president of GAMBRO, you have management responsibility to assure that all devices manufactured or contract manufactured by you or your facilities comply with the Quality System Regulation, Title 21, Code of Federal Regulations (21 CFR Part 820).

The Quality System Regulation requires that each manufacturer prepares and implements quality system procedures adequate to assure that a formally established and documented quality system is developed and has been implemented. It is the responsibility of the highest corporate management to establish the quality policy and to ensure that it is followed. Management with executive responsibility is that level of management that has the authority to establish and make changes to the company quality policy. We consider you and the management located at the corporate headquarters office listed at the above address to be the highest management individuals in your organization; and therefore, the most responsible and accountable for the actions of all other corporate manufacturing sites including, but not limited to, those listed above.

The above-stated inspections revealed that dialysis devices manufactured by GAMBRO, are adulterated, in that the methods used in, or the facilities or controls used for the manufacture, packaging, storage, or installation are not in conformance with the Quality System Regulation; as specified in 21 CFR, Part 820 for the following reasons:

As required by 21 CFR, 820.20, one of the most important responsibilities of management is to establish its policy and objectives for, and commitment to quality. Observations made during these recent inspections indicates that management with executive responsibility failed to ensure that the corporate quality policy is understood, implemented, and maintained at all levels of the organization, in that, a total of six Warning Letters have been issued to you and GAMBRO since 1992, covering the four locations described above.

An example of our concerns regarding corporate oversight and management response to corrective and preventive action involve the manufacture of COBE CentrySystem 3 (C3) Blood Tubing Sets (BTS) with reversed diaphragms at the Newport News facility, which could potentially cause hemolysis of red blood cells. We have no evidence that your Tijuana facility, which manufactures the same product, was sensitized to this situation or potential defect. You have therefore failed to ensure that the problems at your Newport News facility would not be duplicated at another one of your manufacturing sites.

Your July 30 Newport News response does not address the above issue. Your August 7 reply to the three (3) inspections which took place at Lakewood, Tijuana, and Newport News describes management's responsibility but does not include a commitment to corporate oversight and responsibility over individual GAMBRO facilities so as to ensure implementation of the quality policy as described in your letter. For example, your August 7th response states that you will communicate or share trending data about potential problems between facilities which manufacture the same device, however, this does not include corporate commitment to act upon or implement any findings.

Additionally, as responsible management, you have failed to assure that the C3 BTS cartridges meet specifications, in that, the acceptance criteria for filters used in the manufacture of the very same device are different for the Tijuana, and Newport News manufacturing facilities.

As required by 21 CFR 820.100, each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. Investigation has revealed you failed to identify the actions needed to correct and prevent recurrence of non-conforming product, to validate and/or verify such actions to assure effectiveness, to adequately investigate the cause of non-conformities relating to the product and to take all data into account to assure the corrective action is appropriate.

For example, your firm initiated a recall of C3 BTS in 1995 for occluded saline ports. You have received complaints involving occluded blood tubing sets through June 17, 1998. The corrective action taken subsequent to the 1995 recall for the same problem did not appear to be adequate so as to prevent further incidents of occlusion in the blood tubing sets (Newport News and Tijuana) which resulted in the most recent Class I recalls.

Another example involves failure to have written procedures for corrective actions taken to assure proper manual insertion of filters into the C3 cartridges which was neither verified or validated to determine any possible effect the corrective action may have had on the finished device (Newport News).

Other corrective and preventive action situations include failure to establish a rationale for the number of C3 BTS units used to screen for reversed diaphragms (Newport News); preparation and review of trend reports do not include or consider the data for all occurrences (Lakewood, Newport News, and DeLand); your failure to investigate the cause of scrapped C3 BTS cartridges due to burst test failures for Lot #06DNUE202 (Tijuana); and in 1998, in-process occlusions of ports were detected in the new version of the C3 BTS cartridges and investigation as to the cause of the occlusions was inadequate with regards to the [redacted] process. (Tijuana)

Your July 30, reply to our investigation at Newport News states an [redacted], ("[redacted]"), will be implemented to cover rework procedures, however, there is no discussion of validation of the process changes, or a proposed timeframe for completion. Additionally, that reply fails to address the rationale used by your firm to determine the number of units needed to screen for the reversed diaphragm issue. Your July 7, reply regarding the Tijuana inspection is deficient in that you fail to address root causes of failures of the cartridges during burst testing, and your August 7, reply for the Lakewood, Tijuana, and Newport News facilities fails to address corporate oversight of trending activities. Furthermore, your July 7 and 10 responses do not address that the new [redacted] process, implemented to prevent occlusions, has/or will be validated or that you will continue 100% inspection.

As required by 21 CFR 820.198, complaint procedures have not been established and maintained at all locations above for the following: returned goods authorization activities performed by the BTS Complaint Coordinator; processing complaints received by the Quality Audits Centers (QACs) including failure to obtain devices and/or labeling related to the complaint and documenting complaints in the telephone log. For example, of [redacted] complaints reviewed, only [redacted] complaints indicated that devices were returned even though all [redacted] complaints state that devices were available for return. In addition, you failed to maintain records related to complaints as part of the complaint file, including analyses and failure investigations for cracking and leaking cartridges for Lot #61745N (Newport News). Also, complaint files in Lakewood and Tijuana were found to contain discrepancies involving the same complaint (Lakewood).

You failed to promptly review, evaluate and investigate any complaint that represents an event, which must be reported to FDA. For example, complaint receipt dates are not maintained at the various QACs used by Tijuana because the documents received are

discarded. The dates assigned to complaints reflect the date when initially received at Lakewood, rather than the actual date of the complaint when received as received by your manufacturing facilities (Lakewood).

Regarding the two observations above, it is unclear from the August 7 response pertaining to complaint handling, that your proposed system will correct complaint discrepancies between facilities; maintain all information accurately; instruct employees to obtain returned devices, and assure timely processing of complaints. Upon implementation of the new system, we will determine its adequacy. Please justify the implementation date of November 1998.

Records from [redacted], the contract manufacturer of the [redacted], were not obtained during the failure investigation, which should have been issued to document the low conductivity of acid concentrate used in the manufacture of dialysate, (DeLand), and it appears your response dated June 25 is inadequate in that these records from the contract manufacturer are not available for our review.

As required by 21 CFR 820.70, each manufacturer shall develop, conduct, control and monitor production processes to ensure that a device conforms to its specifications. Recent inspection at DeLand, revealed the process change of replacing the [redacted] and [redacted] system on the line was not documented or approved according to procedures. Additionally, on June 2, an employee at the Tijuana facility was observed to retest and accept some cartridges that originally were failed by the leak tester, yet procedures do not allow for retesting and accepting failed cartridges.

We acknowledge your ongoing validation of the labeling equipment at DeLand and will evaluate it during the next inspection at that facility. Regarding retesting, we continue to be concerned that the employee in Tijuana, was able to restart the tester after component rejection and ultimately passed the cartridge as acceptable.

As required by 820.90, each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. Recent inspection of your Newport News facility indicates you failed to document the justification for use of non-conforming devices, cartridge filters, and failed to obtain the signature of the individual(s) authorizing such use. You continued to ship non-conforming product to Tijuana after receiving reports that the cartridge filters were not seated properly and contained flash in the filter windows (pores).

Your July 30, response is inadequate in that you did not indicate how your new corporate "[redacted]", which appears to be a general quality system, will be implemented in each of these individually managed facilities, with unique processes and products being manufactured. Additionally, please justify the implementation date of April 1999.

As required by 21 CFR Part 820.75, where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures.

Our inspections revealed your firm has failed to validate the [redacted] process for the filter component of the C3 BTS cartridge, or the [redacted] used to [redacted] for the C3 cartridge. Additionally, the alarm for the [redacted]

Machine used in the cartridge manufacturing cell was not verified; and the validation for the diaphragm loading station, dated August 29, 1996, did not include parameters for all worst case conditions, i.e., reversed diaphragms (Newport News).

Your July 30 response to the Newport News inspection is inadequate in that validation has not been completed.

Another example of incomplete validation was revealed during the inspection at the dialysate manufacturing facility in DeLand where the [redacted] system was not completely validated.

Your July 30, response indicates that the various validation processes at Newport News have not been completed. FDA will check on the progress of the promised implementation of the validation/verification process for the [redacted] system described in your June 25, reply during the next inspection. Please justify your one-year seasonal performance qualification stage. Our concern lies with distribution of finished product prior to completion of a validated process.

As required by 820.22, you are responsible for establishing procedures for planning and implementing internal quality audits to verify whether quality activities and related results comply with Quality System Regulation and determine the effectiveness of your quality system.

You have failed to establish such audit procedures in that procedures for conducting quality audits at the Lakewood facility do not ensure that all complaint handling activities (including those of your other facilities) are considered and evaluated as appropriate. For example, internal quality audits pertaining to complaint handling of the BTS devices, which are manufactured in Tijuana and Newport News, have never been scheduled or conducted.

Although your July 24, response appears to adequately address the inclusion of Tijuana and Newport News in your internal quality audit, your DeLand facility is not included nor are any other pertinent GAMBRO Healthcare, Inc., locations included. Additionally, since Lakewood is responsible for evaluating and processing corporate Medical Device Reporting (MDR) evaluation activities, you are also responsible for providing and assuring complete oversight of all of your facilities regarding internal audit activities to assure that information between facilities is shared and appropriate action is implemented in a timely manner.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. Several of the deviations noted above, have been observed during previous inspections of your facilities. It is your responsibility to ensure adherence to each requirement of the Act and appropriate regulations. As stated earlier, we are concerned that the specific violations noted in this letter and in the Form FDA-483s issued at the close of the above mentioned inspections are symptomatic of serious underlying systematic problems in your firm's manufacturing and quality assurance systems.

You are responsible for investigating and determining the causes of the violations identified by the FDA. Since the FDA has determined that the causes of these problems appear to be systems problems, you must promptly initiate appropriate permanent corrective actions. Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your letters: dated June 25, addressed to the Orlando District Office; July 7, July 10, and July 24, addressed to the Denver District Office; July 30, addressed to the Baltimore District Office; and August 7, 1998, addressed to Denver and Baltimore Districts and the Center for Devices and Radiological Health, in response to observations noted on the form FDA 483s issued at the conclusion of our inspections at Lakewood, Tijuana, Newport News, and DeLand. We have reviewed your responses and determined some appear to adequately address the observations, and such replies will be further assessed during subsequent inspections at your firm's facilities. The majority of your replies, however, are considered inadequate as articulated throughout this letter.

These outstanding deficiencies are of significant concern to us. You should take prompt action to correct these deviations whether identified by our investigators or your internal systems audit. Failure to promptly correct these deviations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

You should notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to the Food and Drug Administration, Regina Barrell, Compliance Officer.

Sincerely yours,

Gary C. Dean
Director, Denver District

cc: Mr. Michael J. Bikowski
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